

LISTING OF CLAIMS

Please amend the following claims:

1. (original) Method for identifying and/or the producing an effector of a calmodulin-dependent peptidyl-prolyl *cis/trans* isomerase (CaMAP) consisting of the following steps:
 - (a) mixing of appropriate amounts of a CaMAP or a CaMAP peptide fragment/derivative with an appropriate amount of calmodulin or of a calmodulin fragment/derivative in an appropriate reaction solution with and without the effector;
 - (b) adding an appropriate amount of an appropriate CaMAP substrate,
 - (c) measuring CaMAP activity; and
 - (d) detecting that the effector is
 - (i) an inhibitor if the CaMAP activity in the reaction solution with the effector is lower than in the reaction solution without the effector; or
 - (ii) an activator if the CaMAP activity in the reaction solution with the effector is higher than in the reaction solution without the effector.
2. (original) Method for screening and/or producing an effector of a CaMAP consisting of the steps of
 - (a) mixing appropriate amounts of a CaMAP or a CaMAP peptide fragment/derivative with an appropriate amount of calmodulin or a calmodulin fragment/derivative in an appropriate reaction solution with and without a sample containing a single or a multitude of compounds which are candidates for an inhibitor or an activator;
 - (b) adding an appropriate amount of an appropriate CaMAP substrate;
 - (c) measuring CaMAP activity; and
 - (d) detecting that the sample

- (i) exhibits inhibitory activity if the CaMAP activity in the reaction solution with the sample is lower than in the reaction solution without the sample; or
 - (ii) exhibits activating activity if the CaMAP activity in the reaction solution with the sample is higher than in the solution without the sample.
3. (original) Method according to claim 2, further comprising step
- (e) fractioning of the sample for which inhibitory or activating activity was detected in step (d) and repeating of steps (a) to (d) until the inhibitor or activator contained in the sample is present in purified form.
4. (currently amended) Method according to claim 1, wherein the CaMAP is selected from the group consisting of the human CaMAPs FKBP36 (SEQ ID NO: 5), FKB₈ HUMAN, SEQ ID NO: 6, FKB₄₄, FKB₅₁ (FKB₅ HUMAN, SEQ ID NO: 7), FKB₅₂ (FKB₄ HUMAN, SEQ ID NO: 8), and Cyp40 (CYP4 HUMAN, SEQ ID NO: 9), and enzymes that are listed in the "Swiss-Prot" database corresponding to the denotation used in this database under FKB₆₆ (SEQ ID NO: 10), FKB₄₂ (SEQ ID NO: 11), AIP_HUMAN (SEQ ID NO: 12), AIP_CERAE (SEQ ID NO: 13), AIP_MOUSE (SEQ ID NO: 14), AIPL₁_HUMAN (SEQ ID NO: 15), AIPL₁_RAT AIPL₁_RAT (SEQ ID NO: 16), AIPL₁_MOUSE AIPL₁_MOUSE (SEQ ID NO: 17), AIPL₁_RABIT, FKB₈_HUMAN, FKB₈_MOUSE (SEQ ID NO: 18), FKB₅_HUMAN, FKB₅_MOUSE (SEQ ID NO: 19), FKB₄_HUMAN, FKB₄_MOUSE (SEQ ID NO: 20), FKB₄_RABIT (SEQ ID NO: 21), FKB₇_WHEAT (SEQ ID NO: 22), and CYP4_BOVIN (SEQ ID NO: 23), and CYP4_HUMAN.
5. (currently amended) Method according to claim 1, any one of claims 1 to 4, wherein the calmodulin or the calmodulin fragment/derivative is selected from the group consisting of

CALM_ACHKL (P15094, SEQ ID NO: 24), CALM_BLAEM (Q9HFY6, SEQ ID NO: 25), CALM_CANAL (P23286, SEQ ID NO: 26), CALM_CAPAN (P93087, AF65511, SEQ ID NO: 27), and CALM_CAVIAR (P23287, SEQ ID NO: 28).

Applicants: Fischer, et al.

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For: METHOD FOR IDENTIFYING AND PRODUCING EFFECTORS OF CALMODULIN-DEPENDENT PEPTIDYL-PROLYL CIS/TRANS ISOMERASES

Examiner: Shen, Bin

Group Art: 1657

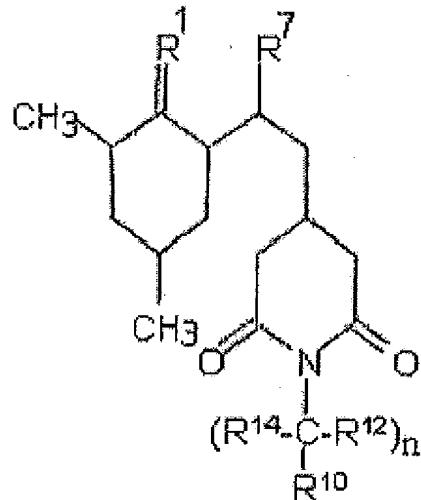
Docket No. VOS0068/US

SEQ ID NO: 27), CALM_CHLRE (P04352, SEQ ID NO: 28), CALM_DICDI (P02599, SEQ ID NO: 29), CALM_DROME (P07181, AAO25039, AAM50750, SEQ ID NO: 30), CALM_ELEEL (P02594, SEQ ID NO: 31), CALM_EMENI (P19533, P60204, SEQ ID NO: 32), CALM_EUGGR (PI1118, SEQ ID NO: 33), ALM_FAGSY (Q39752, SEQ ID NO: 34), CALM_HELAN (P93 I71, SEQ ID NO: 35), CALM_HORVU (P13565, P62162, SEQ ID NO: 36), CALM_HUMAN (P02593, P62158, AAP88918, AAP35501, AAP35464, AAC83174, AAD45181, AAH47523, Q96HK3, SEQ ID NO: 37), CALM_KLULA (O60041, SEQ ID NO: 38), CALM_LYCES CALM_SOLLC (P27161, SEQ ID NO: 39), CALM_LYTPI (P05935, SEQ ID NO: 40), CALM_MAGGR (Q9UWF0, SEQ ID NO: 41), CALM_MAIZE (P41040, SEQ ID NO: 42), CALM_MALDO (P48976, SEQ ID NO: 43), CALM_MEDSA (P17928, SEQ ID NO: 44), CALM_METSE (P02596, Q95NR9, SEQ ID NO: 45), CALM_NEUCR (Q02052, P61859, SEQ ID NO: 41), CALM_ORYSA (P29612, SEQ ID NO: 36), CALM_PARTE (P07463, SEQ ID NO: 46), CALM_PATSP (P02595, SEQ ID NO: 47), CALM_PHYIN (P27165, SEQ ID NO: 48), CALM_PLAFA (P24044, SEQ ID NO: 49), CALM_PLECO (P11120, SEQ ID NO: 50), CALM_PNECA (P41041, SEQ ID NO: 51), CALM_PYUSP (P11121, SEQ ID NO: 52), CALM_SCHPO (P05933, SEQ ID NO: 53), CALM_SOLTU (P13868, SEQ ID NO: 54), CALM_SPIOL (P04353, SEQ ID NO: 55), CALM_STIJA (P21251, SEQ ID NO: 56), CALM_STRPU (P05934, SEQ ID NO: 57), CALM_STYLE (P27166, SEQ ID NO: 58), CALM_TETPY (P02598, SEQ ID NO: 59), CALM_TETTH (Q05055, SEQ ID NO: 60), CALM_TRYBB (P04465, P69097, SEQ ID NO: 61), CALM_TRYCR (P18061, SEQ ID NO: 62), CALM_WHEAT (P04464, SEQ ID NO: 63), CALM_YEAST (P06787, SEQ ID NO: 64), Q9UWF0, Q02052, P19533, AAL89686 (SEQ ID NO: 32), Q7M510, Q96TN0 (SEQ ID NO: 65), P27165, AAG01043 (SEQ ID NO: 48), P02593, Q7T3T2 (SEQ ID NO: 66), Q40302 (SEQ ID NO: 67), O02367 (SEQ ID NO: 68), Q95NR9, Q9UB37 (SEQ ID NO: 69), AAH54805, AAH54973 (SEQ ID NO: 37), AAL02363 (SEQ ID NO: 37), CALM_DANRE (AAH59427, AAH59500, AAH54600, AAH53150, AAH50926, AAH45298, AAH44434, SEQ ID NO: 37), AAP88918, AAP35501, AAP35464, BAC56543 (SEQ ID NO: 37), AAC83174, CALM_RAT (AAD55398, AAH58485, SEQ ID NO: 37), AAC63306 (SEQ ID NO: 37), AAD45181, CALM_MOUSE (AAH21347, BAC40168, BAB28631, BAB28319, BAB28116, BAB23462, AAH58485, AAH51444, Q9D6G4, SEQ ID NO: 37), AAH47523, P07481, Q7QGY7 (SEQ ID NO: 70), Q8STF0 (SEQ ID NO: 71), AAO25039, AAM50750, AAK61380 (SEQ ID NO: 30), BAB89360 (SEQ ID NO: 37)

NO: 30), O94739 (SEQ ID NO: 72), P02594, Q9D6G4, O16305 (SEQ ID NO: 73), Q96HK3, P11120, O96102 (SEQ ID NO: 74), P21251, Q9U6D3 (SEQ ID NO: 75), Q8X187 (SEQ ID NO: 76), O93410 (SEQ ID NO: 77), AAR10240 (SEQ ID NO: 78), P11121, Q9XZP2 (SEQ ID NO: 79), Q42478 (SEQ ID NO: 80), AAQ01510 (SEQ ID NO: 30), P17928, P93171, O97341 (SEQ ID NO: 81), O96081 (SEQ ID NO: 82), AAD10244 (SEQ ID NO: 44), AAM81203 (SEQ ID NO: 44), AAA34238 (SEQ ID NO: 44), AAA34014 (SEQ ID NO: 44), AAA34013 (SEQ ID NO: 44), P02596, P93087, Q43699 (SEQ ID NO: 83), CAD20351 (SEQ ID NO: 27), BAB61916 (SEQ ID NO: 27), BAB61915 (SEQ ID NO: 27), AAF65511, P02595, P59220 (SEQ ID NO: 84), P27162 (SEQ ID NO: 84), Q93VL8 (SEQ ID NO: 85), Q39447 (SEQ ID NO: 86), Q94801 (SEQ ID NO: 87), AAQ63462 (SEQ ID NO: 88), AAQ63461 (SEQ ID NO: 88), AAM81202 (SEQ ID NO: 84), BAB61918 (SEQ ID NO: 84), BAB61917 (SEQ ID NO: 84), BAB61914 (SEQ ID NO: 84), BAB61913 (SEQ ID NO: 84), BAB61912 (SEQ ID NO: 84), BAB61911 (SEQ ID NO: 84), BAB61910 (SEQ ID NO: 84), BAB61909 (SEQ ID NO: 84), AAG27432 (SEQ ID NO: 84), and AAG11418 (SEQ ID NO: 84)

6. (previously presented) Method according to claim 1, wherein the appropriate reaction solution contains bivalent ions selected from the group consisting of Zn^{2+} , Cu^{2+} , Co^{2+} , Ni^{2+} , Mn^{2+} , Ca^{2+} and/or Mg^{2+} at a concentration of 0,1 to 20 mM.
7. (previously presented) Method according to claim 1, wherein the appropriate reaction solution has a pH of between pH 5 and pH 10.
8. (original) Method for identifying and/or producing an effector of a CaMAP consisting of the steps
 - (a) mixing appropriate amounts of a constitutively active CaMAP in an appropriate reaction solution with and without effector;
 - (b) adding an appropriate amount of an appropriate CaMAP substrate;
 - (c) measuring CaMAP activity; and
 - (d) detecting that the effector is

- (i) an inhibitor if the CaMAP activity in the reaction solution with the effector is lower than in the reaction solution without the effector; or
 - (ii) an activator if the CaMAP activity in the reaction solution with the effector is higher than in the reaction solution without the effector.
9. (previously presented) Method according to claim 1, wherein steps (a) and (b) are interchanged.
10. (previously presented) Method according to claim 1, wherein the detection is carried out by spectroscopic or radioactive methods.
11. (previously presented) Method according to claim 1, wherein the method is a high-throughput method.
12. (previously presented) Method according to claim 1, further comprising step (f) formulating the identified and/or produced effector with a pharmaceutically acceptable carrier or solvent.
13. (previously presented) Compound identified according to the method of claim 1, wherein the effector is a cycloheximide derivative having the general formula (1):



in which n is an integer from 1 to 20; R¹² independently is a hydrogen atom, an alkyl residue or an aryl residue,

R¹ is selected from an oxygen atom, a sulfur atom, or the groups NR², NOR² and N-NR²R³, wherein

- (a) R² and R³, independently from each other, are a hydrogen atom, aryl or alkyl, respectively, which can optionally be interrupted by O, S, NH, NR⁵, aryl, heteroaryl, cycloalkyl, heterocycloalkyl or can optionally be substituted by R⁶, or
- (b) R² and R³, together, are C₁-C₆-alkylene, which can optionally be interrupted by O, S, NH, NR⁵, aryl, heteroaryl, cycloalkyl or heterocycloalkyl or can optionally be substituted by R⁶, wherein R⁵ is an alkyl residue or an aryl residue,
R⁶ stands for a hydrogen atom, alkyl, aryl, OR⁵, C(O)OR⁵, CN, F or Cl, wherein R⁵ is defined as above,

R⁷ is a -OH, -OR⁹, -OC(O)R⁹, -OC(S)R⁹, -OC(O)NHR⁹ or -OC(S)NHR⁹ residue, wherein

R⁹ is an alkyl residue which can optionally be interrupted by O, S, NH, NR⁵, aryl, heteroaryl, cycloalkyl or heterocycloalkyl or can optionally be substituted by R⁶ as defined above, or alternatively

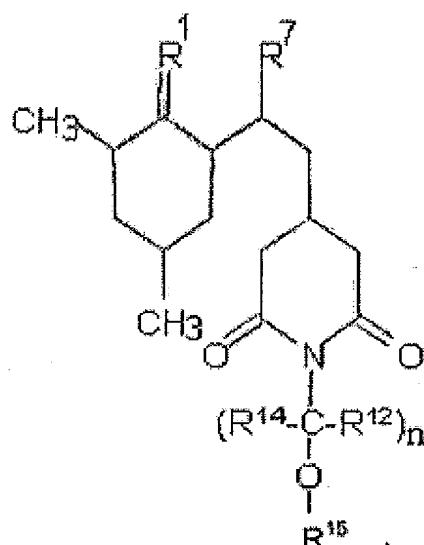
R⁹ is an aryl residue which can optionally be interrupted by O, S, NH or NR⁵ or can optionally be substituted by R⁶ as defined above,

R¹⁰ is a -NHR², -NR²R³, -C(O)OR², -C(S)OR², -C(O)NR²R³, -CN, -NR²C(O)NR²R³, -OC(O)NR²R³, -NR²C(S)NR²R³, -OC(S)NR²R³, or OR², C(O)NHR¹¹ residue, wherein R² and R³ are defined as above,

R¹¹ stands for an amino acid residue or an oligopeptide residue and

R¹⁴ is an alkyl residue or an aryl residue.

14. (previously presented) Compound identified according to the method of claim 1, wherein the effector is a cyclohexamide derivative having the general formula (1) in which n is an integer of 1 to 20 and exhibiting an ether group between R¹⁵ and the complete molecule as illustrated in formula (2) below,



R^1 is selected from an oxygen atom, a sulfur atom, or the groups NR^2 , NOR^2 and $N-NR^2R^3$, wherein

- (a) R^2 and R^3 , independently from each other, are a hydrogen atom, aryl or alkyl, respectively, which can optionally be interrupted by O, S, NH, NR^5 , aryl, heteroaryl, cycloalkyl, heterocycloalkyl or can optionally be substituted by R^6 , or
- (b) R^2 and R^3 , together, are C_1-C_6 -alkylene, which is optionally interrupted by O, S, NH, NR^5 , aryl, heteroaryl, cycloalkyl or heterocycloalkyl or can optionally be substituted by R^6 , wherein
 R^5 is an alkyl residue or an aryl residue,
 R^6 stands for a hydrogen atom, alkyl, aryl, OR^5 , $C(O)OR^5$, CN, F or Cl, wherein R^5 is defined as above,

R^7 is a -OH, -OR⁹, -OC(O)R⁹, -OC(S)R⁹, -OC(O)NHR⁹ or -OC(S)NHR⁹ residue, wherein

R^9 is an alkyl residue which can optionally be interrupted by O, S, NH, NR^5 , aryl, heteroaryl, cycloalkyl or heterocycloalkyl or can optionally be substituted by R^6 as defined above, or alternatively

R^9 is an aryl residue which can optionally be interrupted by O, S, NH or NR^5 or can optionally be substituted by R^6 as defined above,

R^{11} stands for an amino acid residue or an oligopeptide residue,

R¹⁴ is a hydrogen atom, and

R¹⁵ is a hydrogen atom, an alkyl or an aryl residue.

15. (previously presented) Compound according to claim 13 having the above-identified formula (1) for which the following applies:

- (a) n = 1, 2, 3; R¹= O; R⁷= OH, O(CHR¹²)_nR¹⁰, OC(O)CH₃; R¹⁰= C(O)OCH₃, C(O)OC₂H₅, CN, C(O)NH₂,
- (b) n = 3-10; R¹= O; R⁷= OH; R¹⁰= C(O)NHR¹¹, R¹¹= amino acid residue, oligopeptide residue,
- (c) n = 1, 2, 3; R¹= O; R⁷= OH, O(CHR¹²)_nR¹⁰; R¹⁰= C(O)OCH₃, C(O)OC₂H₅, CN, C(O)NH₂,
- (d) n = 1, 2, 3; R¹= NOH, N-NHPh, N-NHCH₃, N-alkyl, N-benzyl; R⁷= OH, O(CHR¹²)_nR¹⁰; R¹⁰= C(O)OCH₃, C(O)OC₂H₅, CN, C(O)NH₂,
- (e) n = 1, 2, 3; R¹= O; R⁷= OH, O(CHR¹²)_nR¹⁰, OC(O)NH-alkyl, OC(O)NH-cycloalkyl, OC(O)NH-aryl; R¹⁰= C(O)OCH₃, C(O)OC₂H₅, CN, C(O)NH₂.

16. (previously presented) Compound according to claim 13 selected from one of the following compounds:

Applicants: Fischer, et al.

Serial No. 10/587,326

Filing Date: June 4, 2007

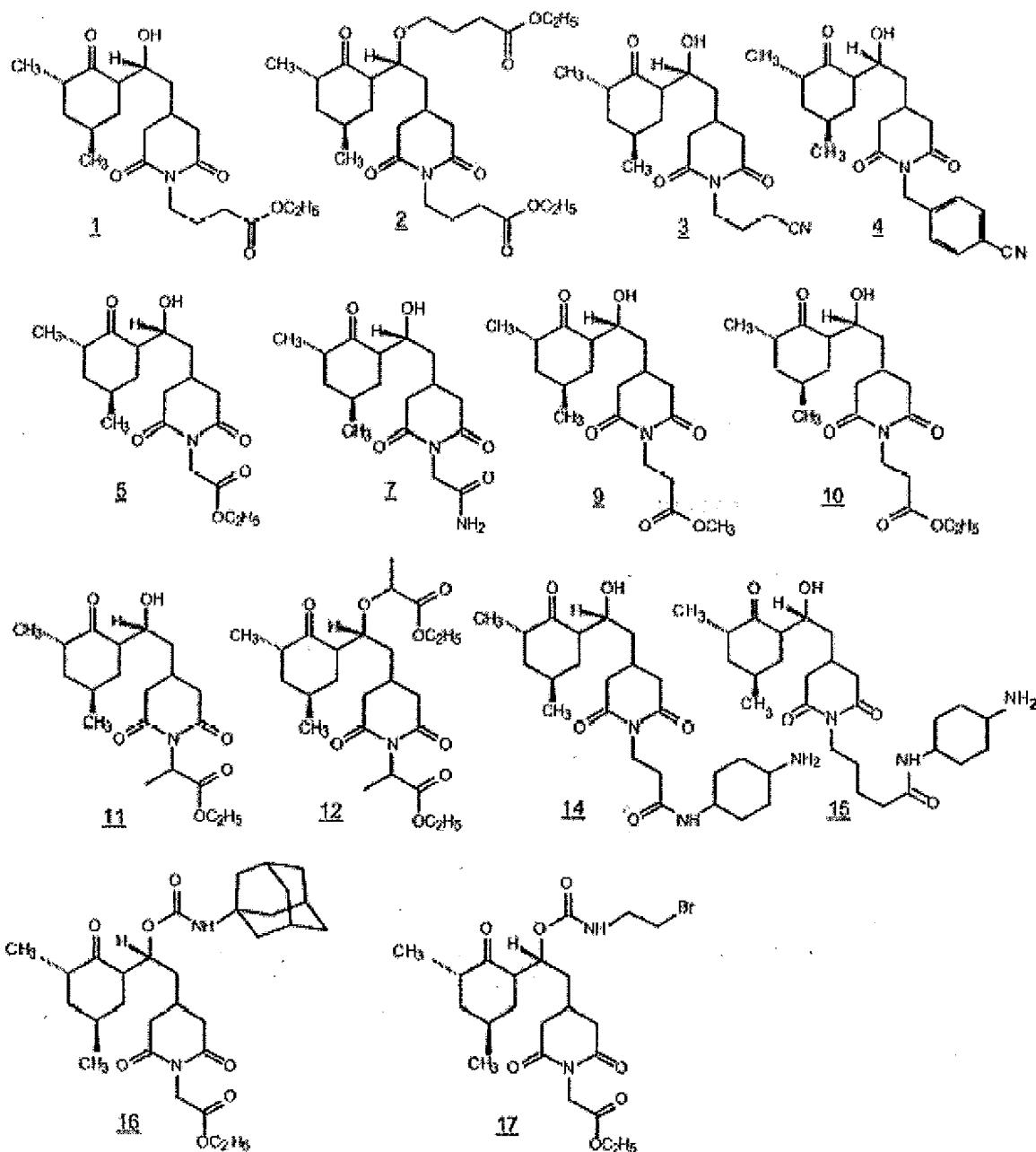
For: METHOD FOR IDENTIFYING AND PRODUCING EFFECTORS OF CALMODULIN-DEPENDENT

PEPTIDYL-PROLYL CIS/TRANS ISOMERASES

Examiner: Shen, Bin

Group Art: 1657

Docket No. VOS0068/US



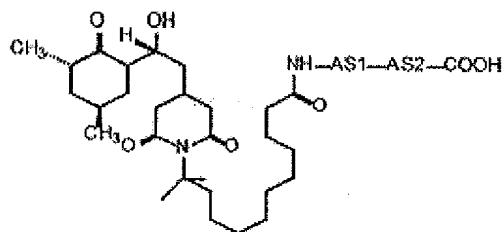
Applicants: Fischer, et al.
Serial No. 10/587,326

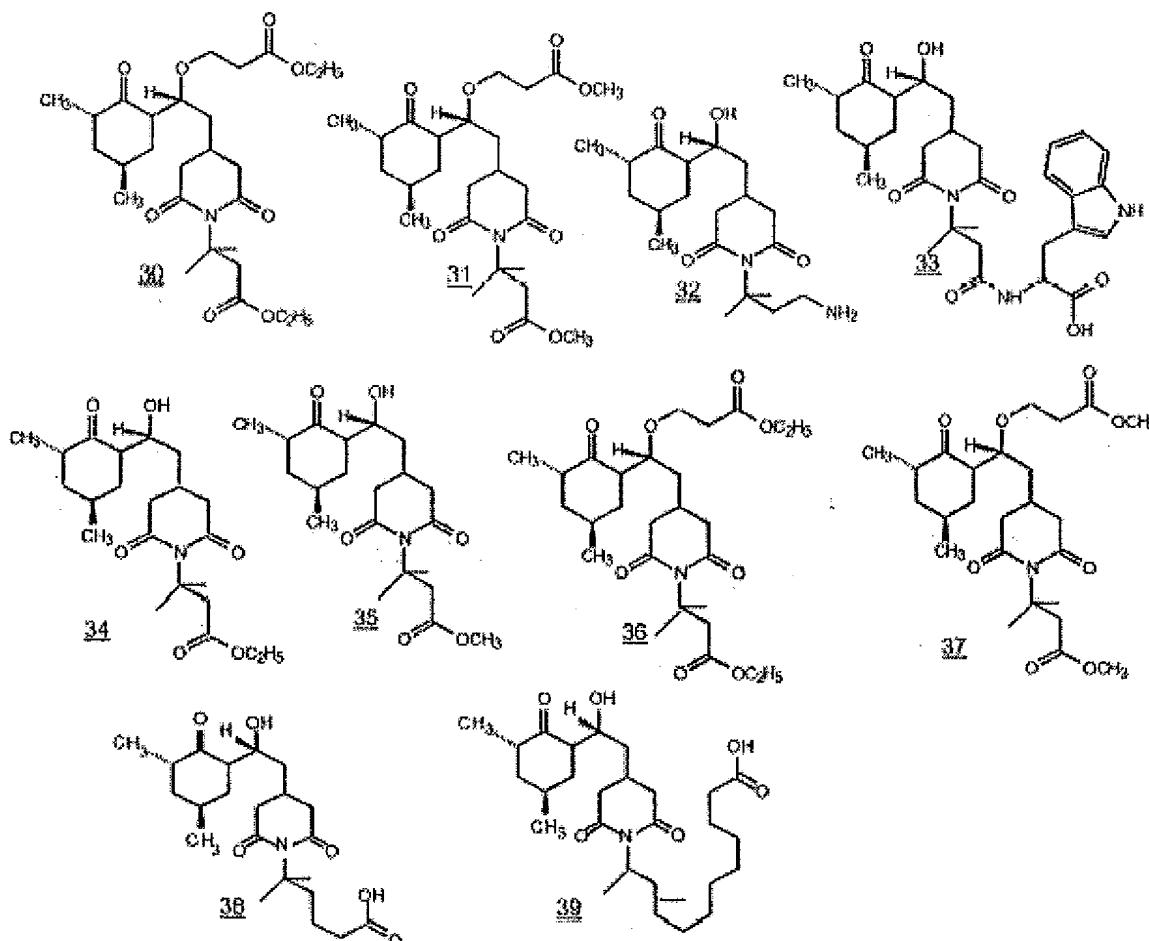
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Examiner: Shen, Bin
Group Art: 1657
Docket No. VOS0068/US

compound	amino acid	amino acid
	residue AS1	residue AS2
<u>18</u>	alanine	alanine
<u>19</u>	valine	alanine
<u>20</u>	tryptophan	alanine
<u>21</u>	isoleucine	alanine
<u>22</u>	methionine	alanine
<u>23</u>	glycine	alanine
<u>24</u>	alanine	valine
<u>25</u>	valine	valine
<u>26</u>	tryptophan	valine
<u>27</u>	isoleucine	valine
<u>28</u>	methionine	valine
<u>29</u>	glycine	valine





17. (previously presented) The effector identified and/or produced by the process of claim 1, optionally with a pharmaceutically acceptable carrier or solvent.
18. (previously presented) A method for the treatment of tumour diseases comprising administering an effector of claim 1 to a patient in need thereof in an amount effective to treat a tumour disease.
19. (previously presented) A method for the inhibition or attenuation of transplant rejection or for the treatment of neurodegenerative diseases comprising administering an effector of claim 1 to a patient in need thereof in an amount effective to inhibit or attenuate transplant rejection or to treat neurodegenerative disease.

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20. (previously presented) A kit comprising CaMAP or a peptide fragment/derivative as described in claim 1 and calmodulin or a calmodulin fragment/derivative as described in claim 1, one or more buffer solutions and/or one or more substrates.